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Note

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Domino strategy for the stereoselective construction of angularly fused tricyclic ethers

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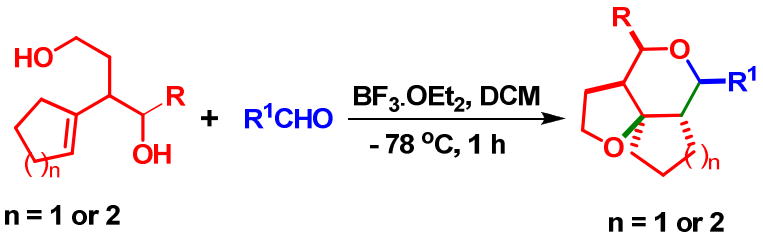


Abstract:

A stereoselective synthesis of decahydrofuro[3,2-*d*]isochromene derivatives has been achieved by the condensation of 2-cyclohexenylbutane-1,4-diol with aldehydes in the presence of a stochiometric amount of $BF_3.OEt_2$ in dichloromethane at -78 °C. Similarly, the condensation of 2-cyclopentenylbutan-1,4-diol with aldehydes provides the corresponding octahydro-2*H*-cyclopenta[*c*]furo[2,3-*d*]pyran derivatives in good yields with high diastereoselectivity. It is an elegant strategy for the quick construction of tricyclic

architectures with four contiguous stereogenic centers in a single-step. **These tricyclic frameworks are the integral part of numerous natural products**.

Polyheterocyclic frameworks are privileged scaffolds in medicinal chemistry. These structures are important synthetic targets for organic chemists due to their prevalence in numerous synthetic and naturally occurring molecules.[1] In particular, angularly fused polyheterocyles have become interesting targets among synthetic community.[2] Moreover, oxygen containing fused structures having characteristic [6-6-5] tricyclic system comprise the core of various naturally occurring molecules that possess a variety of biological activities. For example, Phomactin A is a specific platelet activating factor (PAF) antagonist, which inhibits the PAF-induced platelet aggregation and Neovibsanins are found to display neurite outgrowth activity in PC12 cells (Figure 1).[3] As a result, a few approaches have been described in the literature to construct the relevant scaffolds.[4] However, most of these approaches involve multistep reaction sequence, therefore, it is highly desirable to pursue efficient approaches for the stereoselective construction such skeletons.

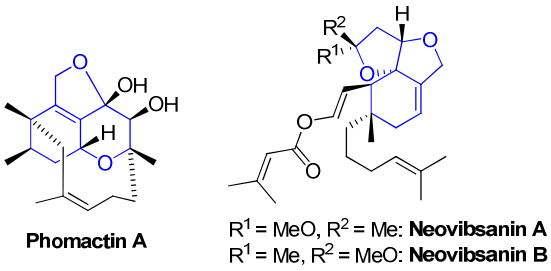


FIGURE 1. Natural products containing tricyclic structures.

The 'Prins cyclization' is a direct and efficient route for the stereoselective construction of tetrahydropyran ring system, which is a backbone of many natural products.[5] In particular, its intramolecular version has become very popular for the stereoselective synthesis of fused and

bridged oxacycles.[6,7] Furthermore, it has been successfully applied in the total synthesis of biologically active natural products.[8]

Following our interests on domino cyclization,[9] we report a novel and efficient strategy for the stereoselective synthesis of decahydrofuro[3,2-*d*]isochromene and octahydro-2*H*-cyclopenta[*c*]furo[2,3-*d*]pyran derivatives. The required enediols (**3**) and (**4**) were prepared by the condensation of diethyl succinate with cyclic ketone under basic conditions. The resulting diesters[10] were reduced under LAH conditions to produce the corresponding enediols (**3**) and (**4**) (Scheme 1).

SCHEME 1. Preparation of starting materials **3** and **4**

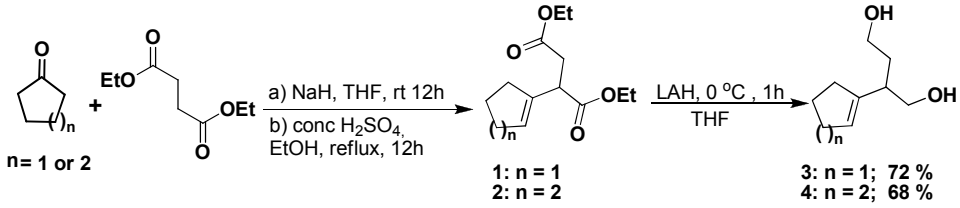
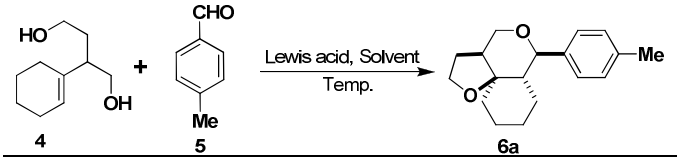


TABLE 1. Optimization of the reaction conditions

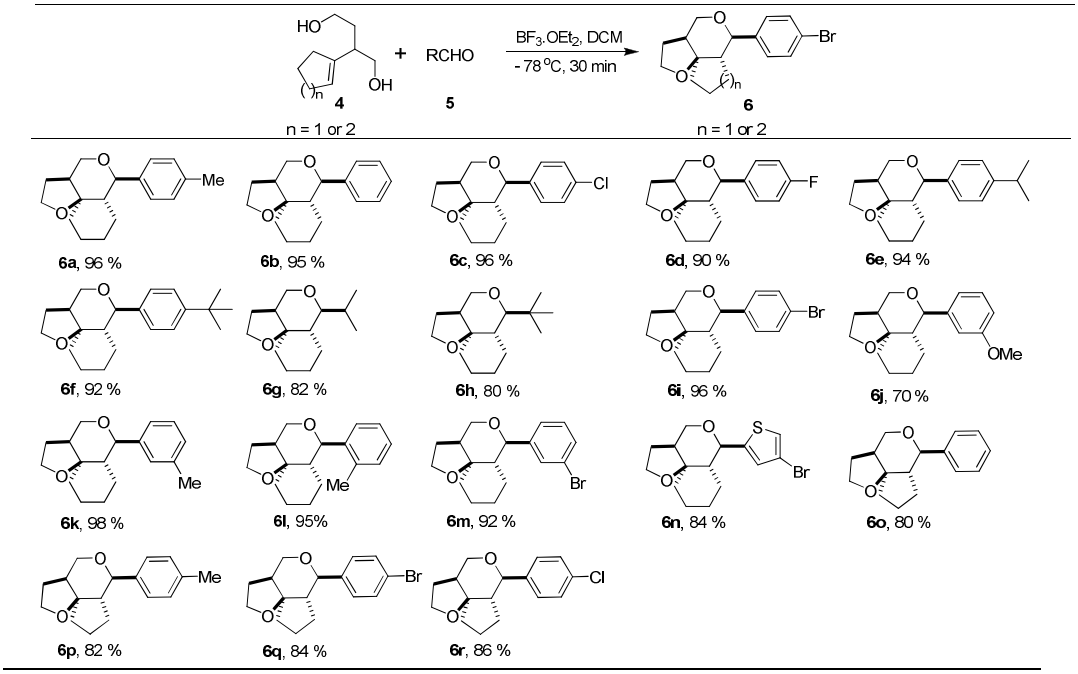


Entry	Lewis/Bronsted acid	Equiv	Solvent	Temp (°C)	Time (h)	Yield (%)[a]
a	**$BF_3{\cdot}OEt_2$**	**1.2**	**DCM**	**-78**	**1**	**95**
b	$BF_3{\cdot}OEt_2$	1.2	DCM	0	1	50
c	$SnCl_4$	1.0	DCM	-78	1	70
d	$TiCl_4$	1.0	DCM	-78	1	60
e	$In(OTf)_3$	1.0	DCM	25	1	50
f	TMSOTf	1.2	DCM	-78	1	mix
g	*p*-TSA	1.0	DCE	80	15	–
h	CSA	1.0	DCE	80	16	–
i	TfOH	1.2	DCM	-78	1	20
j	$BF_3{\cdot}OEt_2$	1.2	THF	-78 to 25	10	–
k	$BF_3{\cdot}OEt_2$	1.2	Benzene	-78 to 25	10	–
l	$BF_3{\cdot}OEt_2$	1.2	CH_3CN	-78 to 25	10	–

[a]Yield refers to pure products after column chromatography.

At the outset, we attempted the coupling of enediol (**4**) (1.0 equiv) with *p*-tolualdehyde (1.2 equiv) in the presence of $BF_3.OEt_2$ (1.2 equiv). The reaction proceeded smoothly at -78 °C with high stereocontrol (entry a, Table 1). However, the reaction was found to be sluggish at 0 ^oC resulting in the decomposition of starting material (entry b, Table 1). Other Lewis acids such as $SnCl_4$, $TiCl_4$ and $In(OTf)_3$ gave the product relatively in lower yields (entries c-e, Table 1), whereas TMSOTf gave the mixture of products (entry f, Table 1). Bronsted acids such as *p*-TSA and CSA failed to initiate the reaction even after long reaction time at elevated temperature (entries g,h, Table 1). Though the reaction was successful with 1.2 equiv of TfOH, the required product was isolated in low yield (entry i, Table 1). We further performed the reaction in different solvents such as THF, benzene and CH_3CN (entries j-l, Table 1). Among them, DCM gave the best results in terms of yield. The structure and relative stereochemistry of **6a** were established by 1D and 2D NMR experiments (Supporting information).

TABLE 2. Synthesis of decahydrofuro[3,2-*d*]isochromene/octahydro-2*H*-cyclopenta[*c*]furo[2,3-*d*]pyran derivatives



Yields refer to the pure products after column chromatography.

The scope of the reaction is further exemplified with diverse aldehydes bearing different substitution pattern on aromatic ring (Table 2). In all the cases, the products were obtained in good yields with high selectivity. It is noteworthy to mention that a wide range of functional groups are well tolerated under the reaction conditions. The functional groups present on aromatic ring had shown some effect on the conversion. It was observed that alkyl substituted aromatic aldehydes gave the products relatively in higher yields than the corresponding halide or methoxy-substituted aldehydes. The reaction is further extended to aliphatic aldehydes (Table 2, **6g** and **6h**) and heterocyclic aldehyde (Table 2, **6n**). This method also works well with sterically hindered substrates such as *p-tert*-butylbenzaldehyde and pivalaldehyde (Table 2, **6f** and **6h**). Therefore, this method is successful with aromatic, aliphatic and heteroaromatic aldehydes to generate the products with diverse substitution pattern. However, the reactions were not successful with ketones like cyclohexanone and acetone.

In order to broaden the scope of this methodology, we studied the effect of substituents on enediol precursor. Accordingly, we prepared a series of substituted enediols adopting the synthetic sequence as outlined in Scheme 2. The intermediate, cyclohexenyl butyrolactone (**7**) was prepared by reacting cyclohexanone with ϒ-butyrolactone.[11] Reduction of lactone **7** with DIBAL-H afforded the lactol **8** in 90% yield, which was then treated with Grignard reagents to produce the substituted enediols **9** with good diastereoselectivity, which was confirmed by NMR. The relative stereochemistry of compound **9** was established as *syn* with respect to -OH and -CH_2CH_2OH groups based on stereochemistry of **10a** which was confirmed by X-ray crystallography. The observed stereochemistry is consistent with a known method,[12] in which *anti*-Cram's stereoselection was explained based on a chelate model **A** (Scheme 2).

SCHEME 2. Preparation of compounds **9a-e**.

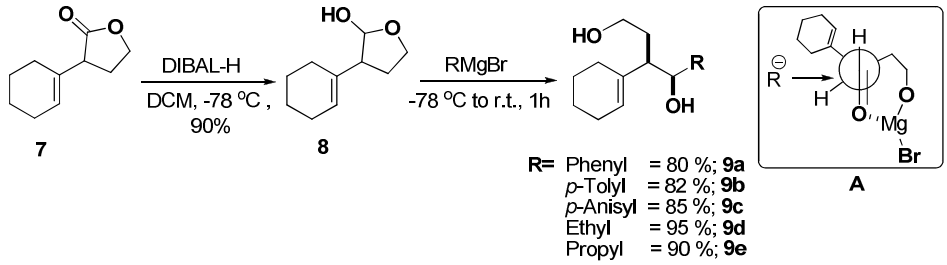
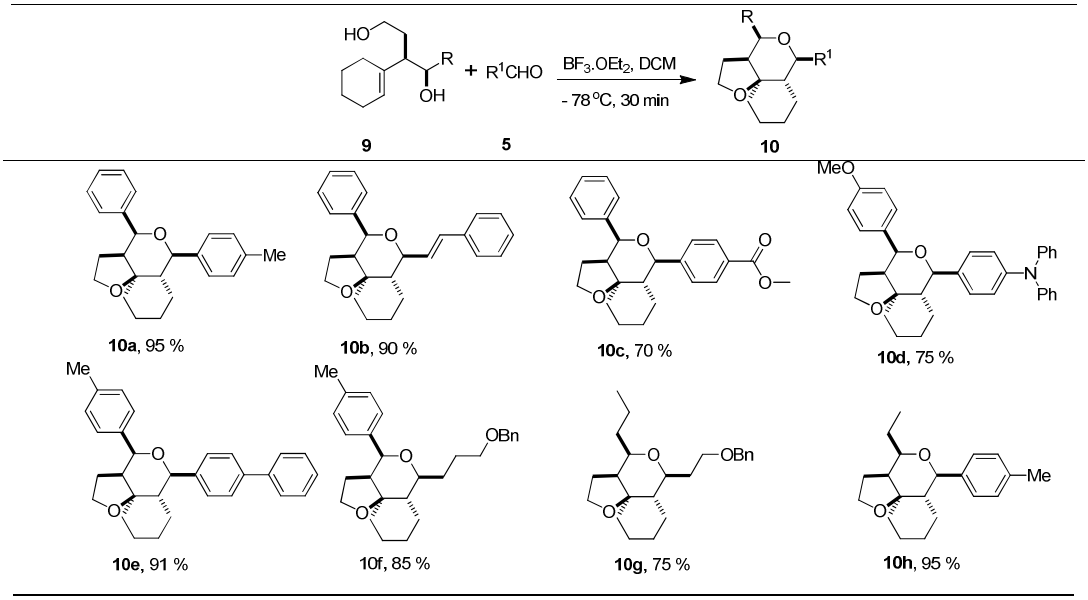


TABLE 3. Synthesis of substituted decahydrofuro[3,2-*d*]isochromene.



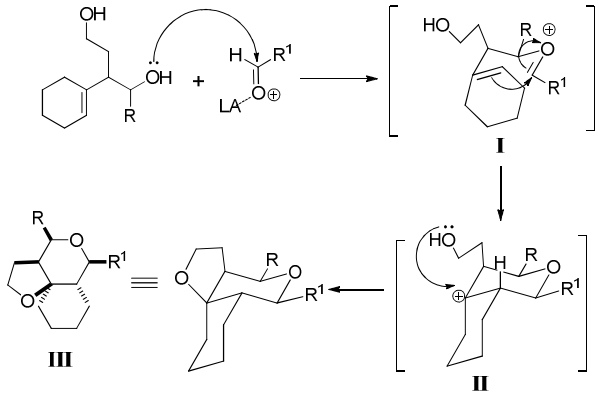
Yields refer to the pure products after column chromatography.

Treatment of various substituted enediols **9** with different aldehydes under optimised conditions gave the corresponding decahydrofuro[3,2-*d*]isochromene derivatives (**10**) in excellent yields (**10a-h**, Table 3). There was no effect of the substituents on stereochemical outcome of the reaction, which was confirmed by a single crystal X-ray diffraction of **10a** (Supporting information). The reaction was quite successful with different aldehydes bearing olefin (**10b**, Table 3), ester (**10c**, Table 3), *N*,*N*-diphenylamino functionality (**10d**, Table 3). Furthermore, aliphatic aldehyde bearing benzyloxy group also participated effectively (**10f** and **10g** Table 3). However, the aliphatic aldehyde having amide functionality (*N*-(3-oxopropyl)benzamide) failed to give the product under similar conditions.

Based on our previous observations,[9] we proposed a plausible reaction mechanism in Scheme 3. The reaction is expected to proceed through the formation of oxocarbenium ion **I** from the condensation of aldehyde with enediol under acidic conditions. The resulting oxocarbenium ion is trapped by an internal olefin leading to the formation of a cyclic carbocation **II**, which is simultaneously neutralized by a tethered hydroxyl group to generate the tricyclic **III** ether as

depicted in Scheme 3. The exceptional diastereoselectivity observed in this process can be explained by a favourable trapping of the more stable carbocation from a less hindered equatorial side to overcome unfavourable 1,3-diaxial interactions.[13]

SCHEME 3. A plausible reaction path way



In conclusion, we have developed a novel strategy for the efficient synthesis of angularly fused tricyclic ethers from aldehydes and enediols using a stoichiometric amount of $BF_3.Et_2O$. It is an elegant approach for the stereoselective synthesis of decahydrofuro[3,2-*d*]isochromene and octahydro-2*H*-cyclopenta[*c*]furo[2,3-*d*]pyran derivatives. This method offers numerous advantages such as good yields, excellent diastereoselectivity, diverse functional group tolerance, and a wide substrate scope, which make it an attractive strategy for the synthesis of biologically relevant structural scaffolds with four contiguous stereogenic centres.

Experimental Section

General. All solvents were dried according to standard literature procedures. The reactions were performed in oven-dried round bottom flasks and the flasks were fitted with rubber septa and the reactions were conducted under a nitrogen atmosphere. Glass syringes were used to transfer solvents. Crude products were purified by column chromatography on silica gel of 60–120 or

100-200 mesh. Thin layer chromatography plates were visualized by exposure to ultraviolet light and/or by exposure to iodine vapors and/or by exposure to methanolic acidic solution of *p*-anisaldehyde followed by heating (<1 min) on a hot plate (~250 °C). Organic solutions were concentrated on rotary evaporator at 35–40 °C. IR spectra were recorded on FT-IR spectrometer. ^{1}H and ^{13}C NMR (proton-decoupled) spectra were recorded in $CDCl_3$ solvent on 200, 300, 400 or 500 MHz NMR spectrometer. Chemical shifts (δ) were reported in parts per million (ppm) with respect to TMS as an internal standard. Coupling constants (*J*) are quoted in hertz (Hz). Mass spectra were recorded on mass spectrometer by Electrospray ionization (ESI) or Atmospheric pressure chemical ionization (APCI) technique.

X-ray Crystallography.

X-ray data for the compounds were collected at room temperature using Smart Apex CCD diffractometer with graphite monochromated MoKα radiation (λ=0.71073Å) with ω-scan method. Preliminary lattice parameters and orientation matrices were obtained from four sets of frames.

Integration and scaling of intensity data was accomplished using SAINT program[14]. The structure was solved by direct methods using SHELXS-2014[15] and refinement was carried out by full-matrix least-squares technique using SHELXL-2014[15]. Anisotropic displacement parameters were included for all non-hydrogen atoms. All H atoms were positioned geometrically and treated as riding on their parent C atoms [C-H = 0.93-0.97 Å and $U_{iso}(H) = 1.5U_{eq}(C)$ for methyl H or $1.2U_{eq}(c)$ for other H atoms]. The methyl groups were allowed to rotate but not to tip.

Typical procedure for domino cyclization

To a mixture of 2-cyclohexenylbutan-1,4-diol (0.5 mmol) and *p*-tolualdehyde (0.6 mmol) in anhydrous DCM (5 mL) was added $BF_3.OEt_2$ (1.2 equiv) at -78 ^{o}C. The resulting mixture was allowed to stir at the same temperature for 1h . After completion, the reaction was quenched with sat. $NaHCO_3$ solution. The organic layer was separated and the aqueous layer was extracted with

dichloromethane (2x5 mL). The organic phases were washed with brine, dried over anhydrous Na_2SO_4 and concentrated in vacuo. The resulting crude product was purified by silica gel column chromatography (100-200 mesh) using ethyl acetate/hexane gradient mixture to afford the pure product **6a** (Table 2, entry a).

6-*p*-Tolyldecahydrofuro[3,2-*d*]isochromene (6a):

Viscous liquid; Yield 130 mg, 96% ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.20 (d, *J* = 8.0 Hz, 2H), 7.14 (d, *J* = 7.9 Hz, 2H), 4.31 (d, *J* = 11.1 Hz, 1H), 4.08 (dd, *J* = 12.3, 0.9 Hz, 1H), 4.0 (td, *J* = 3.2, 8.6 Hz, 1H), 3.91 (q, *J* = 8.3 Hz, 1H), 3.85 (dd, *J* = 3.2, 12.2 Hz, 1H), 2.50-2.42 (m, 1H), 2.33 (s, 3H), 2.10-2.01 (m, 2H), 1.90 (dd, *J* = 5.1, 10.9 Hz, 1H), 1.77-1.71 (m, 1H), 1.69-1.52 (m, 3H), 1.42-1.36 (m, 1H), 1.34-1.24 (m, 2H), 1.05 (d, *J* = 14.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.8, 137.4, 129.0, 126.7, 80.8, 79.8, 66.4, 64.8, 45.3, 41.8, 32.2, 28.1, 23.0, 22.4, 21.1, 21.0; IR (KBr): υ 3019, 2925, 2855, 1216, 1110, 771, 667; HRMS (Orbitrap ESI) calcd for $C_{18}H_{25}O_2$ $[M+H]^+$: 273.1849. Found: 273.1844.

6-Phenyldecahydrofuro[3,2-*d*]isochromene (6b):

Pale yellow liquid ; Yield 122 mg, 95% ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.27 (m, 5H), 4.35 (d, *J* = 10.9 Hz, 1H), 4.10 (dd, *J* = 1.0, 12.3 Hz, 1H), 4.01 (td, *J* = 3.6, 8.6 Hz, 1H), 3.91 (q, *J* = 8.6 Hz, 1H), 3.87 (dd, *J* = 3.2, 12.2 Hz, 1H), 2.52-2.43 (m, 1H), 2.11-2.02 (m, 2H), 1.91 (dd, *J* = 5.1, 10.9 Hz, 1H), 1.78-1.73 (m, 1H), 1.69-1.53 (m, 3H), 1.43-1.38 (m, 1H), 1.35-1.27 (m, 2H), 1.04 (d, *J* = 14.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.8, 128.3, 127.8, 126.8, 81.0, 79.8, 66.4, 64.8, 45.3, 41.9, 32.2, 28.1, 23.0, 22.4, 21.0; IR (KBr): υ 3029, 2925, 2855, 1453, 1218, 1110, 1030, 771, 700; HRMS (Orbitrap ESI) calcd for $C_{17}H_{23}O_2$ $[M+H]^+$: 259.1692. Found: 259.1688.

6-(4-Chlorophenyl)decahydrofuro[3,2-*d*]isochromene (6c):

Viscous liquid; Yield 141 mg, 96% ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.30 (m, 2H), 7.27-7.25 (m, 2H), 4.32 (d, *J* = 11.1 Hz, 1H), 4.09 (dd, *J* = 0.7, 12.3 Hz, 1H), 4.00 (td, *J* = 3.2, 9.0 Hz, 1H), 3.91 (q, *J* = 8.5 Hz, 1H), 3.85 (dd, *J* = 3.2, 12.2 Hz, 1H), 2.49-2.39 (m, 1H), 2.11-1.98 (m, 2H), 1.84 (dd, *J* = 5.0, 10.3 Hz, 1H), 1.78-1.72 (m, 1H), 1.70-1.52 (m, 3H), 1.44-1.38 (m, 1H),

1.31-1.21 (m, 2H), 1.01 (d, *J* = 14.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 139.4, 133.4, 128.5, 128.2, 80.2, 79.6, 66.6, 64.8, 45.2, 42.2, 32.2, 28.1, 22.9, 22.3, 21.0. IR (KBr): υ 3005, 2929, 2856, 1491, 1217, 1108, 1029, 771, 747, 665; HRMS (Orbitrap ESI) calcd for $C_{17}H_{22}ClO_2$ $[M+H]^+$: 293.1302. Found: 293.1297.

6-(4-Fluorophenyl)decahydrofuro[3,2-*d*]isochromene (6d):

Viscous liquid; Yield 124 mg, 90%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31-7.25 (m, 2H), 7.06-7.00 (m, 2H), 4.33 (d, *J* = 10.9 Hz, 1H), 4.08 (dd, *J* = 0.9, 12.2 Hz, 1H), 4.00 (td, *J* = 3.2, 8.6 Hz, 1H), 3.91 (q, *J* = 8.6 Hz, 1H), 3.85 (dd, *J* = 3.2, 12.2 Hz, 1H), 2.49-2.40 (m, 1H), 2.11-1.99 (m, 2H), 1.86 (dd, *J* = 5.1, 10.9 Hz, 1H), 1.78-1.72 (m, 1H), 1.70-1.53 (m, 3H), 1.44-1.38 (m, 1H), 1.32-1.21 (m, 2H), 1.02 (d, *J* = 14.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.8, 160.6, 136.6, 128.4, 128.3, 115.0, 114.5, 80.2, 79.6, 66.4, 64.8, 45.2, 42.1, 32.1, 28.0, 22.9, 22.3, 20.9; IR (KBr): υ 3019, 2933, 2857, 1512, 1215, 742, 667; HRMS (Orbitrap ESI) calcd for $C_{17}H_{22}FO_2$ $[M+H]^+$: 277.1598. Found: 277.1591.

6-(4-Isopropylphenyl)decahydrofuro[3,2-*d*]isochromene (6e):

Pale yellow liquid ; Yield 141 mg, 94%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24-7.18 (m, 4H), 4.32 (d, *J* = 10.9 Hz, 1H), 4.08 (dd, *J* = 1.0, 12.3 Hz, 1H), 4.01 (td, *J* = 3.2, 8.6 Hz, 1H), 3.91 (q, *J* = 8.5 Hz, 1H), 3.85 (dd, *J* = 3.2, 12.2 Hz, 1H), 2.89 (hep, *J* = 6.8 Hz, 1H), 2.52-2.42 (m, 1H), 2.10-2.01 (m, 2H), 1.93 (d, *J* = 5.3, 11.1 Hz, 1H), 1.77-1.71 (m, 1H), 1.70-1.52 (m, 3H), 1.43-1.36 (m, 1H), 1.35-1.25 (m, 2H), 1.23 (d, *J* = 7.0 Hz, 6H), 1.09 (d, *J* = 13.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 148.4, 138.1, 126.8, 126.4, 80.8, 79.8, 66.4, 64.8, 45.3, 41.7, 33.8, 32.2, 28.1, 24.0, 23.9, 23.0, 22.5, 21.0; IR (KBr): υ 3007, 2930, 2859, 1459, 1216, 1108, 771, 745, 665; HRMS (Orbitrap ESI) calcd for $C_{20}H_{29}O_2$ $[M+H]^+$: 301.2162. Found: 301.2155.

6-(4-*tert*-Butylphenyl)decahydrofuro[3,2-*d*]isochromene (6f):

Pale yellow liquid; Yield 144 mg, 92% ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.34 (m, 2H), 7.25-7.22 (m, 2H), 4.32 (d, *J* = 11.1 Hz, 1H), 4.08 (dd, *J* = 1.0, 12.2 Hz, 1H), 4.01 (td, *J* = 3.0, 8.6 Hz, 1H), 3.91 (q, *J* = 8.5 Hz, 1H), 3.85 (dd, *J* = 3.2, 12.2 Hz, 1H), 2.51-2.42 (m, 1H), 2.10-2.01 (m, 2H), 1.93 (dd, *J* = 5.1, 10.9 Hz, 1H), 1.77-1.71 (m, 1H), 1.69-1.52 (m, 3H), 1.43-1.37 (m, 1H), 1.35-1.25 (m, 2H), 1.10 (d, *J* = 14.0 Hz, 1H), 1.30 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ

150.7, 137.7, 126.5, 125.2, 80.7, 79.8, , 66.3, 64.8, 45., 41.6, 34.5, 32.2, 31.3, 28.1, 23.0, 22.5, 21.1; IR (KBr): υ 3018, 2924, 2853, 1462, 1216, 771; HRMS (Orbitrap ESI) calcd for $C_{21}H_{31}O_2[M+H]^+$: 315.2318. Found: 315.2310.

6-Isopropyldecahydrofuro[3,2-*d*]isochromene (6g):

Pale yellow liquid; Yield 91 mg, 82%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.96-3.90 (m, 2H), 3.84 (q, *J* = 8.3 Hz, 1H), 3.63 (dd, *J* = 3.5, 12.0 Hz, 1H), 3.23 (dd, *J* = 2.7, 10.0 Hz, 1H), 2.24-2.15 (m, 1H), 2.00-1.86 (m, 3H), 1.74-1.53 (m, 6H), 1.47-1.40 (m, 2H), 1.23-1.11 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.84 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 81.1, 80.2, 66.1, 64.6, 44.9, 37.7, 32.3, 28.2, 28.1, 23.2, 22.4, 21.1, 20.5, 14.1; IR (KBr): υ 2926, 2855, 1456, 1369, 1222, 1079, 1031, 771, 668; HRMS (APCI) calcd for $C_{14}H_{25}O_2[M+H]^+$: 225.1849. Found: 225.1848.

6-*tert*-Butyldecahydrofuro[3,2-*d*]isochromene (6h):

Pale yellow liquid; Yield 95 mg, 80%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.90 (q, *J* = 7.7 Hz, 1H), 3.84-3.78 (m, 2H), 3.58 (dd, *J* = 4.7, 12.0 Hz, 1H), 2.82 (d, *J* = 6.4 Hz, 1H), 2.20-2.11 (m, 1H), 2.00-1.92 (m, 1H), 1.93-1.86 (m, 1H), 1.83-1.76 (m, 2H), 1.73-1.65 (m, 2H), 1.50-1.24 (m, 5H), 0.95 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 88.6 , 81.8, 69.0, 64.9, 40.4, 39.3, 36.6, 34.9, 32.5, 30.6, 26.5, 24.5, 23.6; IR (KBr): υ 2927, 2855, 1453, 1362, 1218, 1076, 1029, 771, 669; HRMS (Orbitrap ESI) calcd for $C_{15}H_{27}O_2[M+H]^+$: 239.2005. Found: 239.2001.

6-(4-Bromophenyl)decahydrofuro[3,2-*d*]isochromene (6i):

Viscous liquid; Yield 161 mg, 96%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.3 Hz, 2H), 7.19 (d, *J* = 8.3 Hz, 2H), 4.31 (d, *J* = 10.9 Hz, 1H), 4.08 (dd, *J* = 0.9, 12.2, 1H), 3.99 (td, *J* = 3.5, 8.8, 1H), 3.90 (q, *J* = 8.5 Hz, 1H), 3.85 (dd, *J* = 3.2, 12.2, 1H), 2.48-2.39 (m, 1H), 2.11-1.98 (m, 2H), 1.83 (dd, *J* = 5.1, 10.9 Hz, 1H), 1.78-1.72 (m, 1H), 1.70-1.53 (m, 3H), 1.44-1.38 (m, 1H), 1.30-1.23 (m, 2H), 1.01 (d, *J* = 14.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.8, 131.4, 128.5, 121.5, 80.2, 79.6, 66.4, 64.8, 45.1, 42.1, 32.1, 28.0, 22.9, 22.3, 21.0. IR (KBr): υ 2929, 2857, 1487, 1456, 1218, 1109, 1009, 771; HRMS (APCI) calcd for $C_{17}H_{22}BrO_2[M+H]^+$: 337.0797. Found: 337.0784

6-(3-Methoxyphenyl)decahydrofuro[3,2-*d*]isochromene (6j):

Pale yellow liquid; Yield 100 mg, 70%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27-7.25 (m, 1H), 6.90 (d, *J* = 7.4 Hz, 1H), 6.88-6.86 (m, 1H), 6.82 (ddd, *J* = 0.8, 2.5, 8.0 Hz, 1H), 4.31 (d, *J* = 10.9 Hz, 1H), 4.09 (dd, *J* = 1.0, 12.3 Hz, 1H), 4.00 (td, *J* = 3.2, 8.8 Hz, 1H), 3.91 (q, *J* = 8.6 Hz, 1H), 3.85 (dd, *J* = 3.2, 12.2 Hz, 1H), 3.81 (s, 3H), 2.50-2.41 (m, 1H), 2.10-2.00 (m, 2H), 1.89 (dd, *J* = 5.1, 10.9 Hz, 1H), 1.78-1.71 (m, 1H), 1.69-1.52 (m, 3H), 1.44-1.38 (m, 1H), 1.34-1.24 (m, 2H), 1.07 (d, *J* = 14.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.6, 142.3, 129.3, 119.3, 113.0, 112.6, 80.9, 79.7, 66.4, 64.8, 55.1, 45.2, 41.9, 32.2, 28.1, 23.0, 22.4, 21.0. IR (KBr): υ 2925, 2854, 1586, 1455, 1256, 1109, 1029, 772; HRMS (EI) calcd for $C_{18}H_{24}O_3[M]^+$: 288.1725 Found: 288.1730

6-*m*-Tolyldecahydrofuro[3,2-*d*]isochromene (6k):

Pale yellow liquid; Yield 133 mg, 98%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25-7.18 (m, 1H), 7.15-7.06 (m, 3H), 4.31 (d, *J* = 11.1 Hz, 1H), 4.09 (d, *J* = 12.2 Hz, 1H), 4.02 (td, *J* = 3.2, 9.0 Hz, 1H), 3.91 (q, *J* = 8.3 Hz, 1H), 3.85 (dd, *J* = 3.0, 12.4 Hz, 1H), 2.56-2.40 (m, 1H), 2.35 (s, 3H), 2.13-1.99 (m, 2H), 1.92 (dd, *J* = 5.0, 10.9 Hz, 1H), 1.80-1.50 (m, 4H), 1.45-1.23 (m, 3H), 1.06 (d, *J* = 13.7 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.6, 138.0, 128.6, 128.1, 127.3, 124.1, 81.1, 79.8, 66.4, 64.8, 45.3, 41.8, 32.2, 28.1, 23.0, 22.4, 21.4, 21.0; IR (KBr): υ 2924, 2854, 1456, 1219, 1111, 1031, 773; HRMS (Orbitrap ESI) calcd for $C_{18}H_{25}O_2[M+H]^+$: 273.1849. Found: 273.1842.

6-*o*-Tolyldecahydrofuro[3,2-*d*]isochromene (6l):

Pale yellow liquid; Yield 129 mg, 105-107 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 (d, *J* = 7.3 Hz, 1H), 7.23-7.19 (m, 1H), 7.18-7.13 (m, 2H), 4.60 (d, *J* = 11.1 Hz, 1H), 4.08 (dd, *J* = 0.9, 12.2 Hz, 1H), 4.04 (td, *J* = 3.0, 8.8 Hz, 1H), 3.93 (q, *J* = 8.5 Hz, 1H), 3.85 (dd, *J* = 3.2, 12.3 Hz, 1H), 2.55-2.44 (m, 1H), 2.42 (s, 3H), 2.13-2.00 (m, 3H), 1.79-1.73 (m, 1H), 1.69-1.55 (m, 3H), 1.44 (d, *J* = 14.4 Hz, 1H), 1.32-1.19 (m, 2H), 1.06 (d, *J* = 14.1 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.9, 135.9, 130.4, 127.5, 126.8, 126.3, 79.9, 66.5, 65.0, 45.5, 40.9, 32.6, 29.7, 28.2, 23.0, 22.5, 22.1, 19.7; . IR (KBr): υ 3006, 2932, 2859, 1458, 1217, 1107, 1029, 745, 666 ; HRMS (Orbitrap ESI) calcd for $C_{18}H_{25}O_2[M+H]^+$: 273.1849. Found: 273.1844

6-(3-Bromophenyl)decahydrofuro[3,2-*d*]isochromene (6m):

Pale yellow liquid; Yield 154 mg, 92% ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.49-7.47 (m, 1H), 7.44-7.40 (m, 1H), 7.24-7.19 (m, 2H), 4.31 (d, *J* = 10.9 Hz, 1H), 4.09 (dd, *J* = 1.0, 12.3 Hz, 1H), 4.01 (td, *J* = 3.2, 8.6 Hz, 1H), 3.91 (q, *J* = 8.5 Hz, 1H), 3.85 (dd, *J* = 3.3, 12.3 Hz, 1H), 2.49-2.40 (m, 1H), 2.11-1.98 (m, 2H), 1.85 (dd, *J* = 5.1, 10.9 Hz, 1H), 1.79-1.73 (m, 1H), 1.71-1.52 (m, 3H), 1.47-1.40 (m, 1H), 1.33-1.21 (m, 2H), 1.04 (d, *J* = 14.0 Hz, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.1, 130.9, 129.8, 125.7, 122.6, 79.6, 66.4, 64.9, 45.2, 42.0, 32.1, 28.0, 22.9, 22.3, 21.1. IR (KBr): υ 3015, 2931, 2858, 1569, 1216, 1109, 1216, 1109, 1028, 747, 667; HRMS (APCI) calcd for $C_{17}H_{22}BrO_2[M+H]^+$: 337.0797. Found: 337.0788

6-(4-Bromothiophen-2-yl)decahydrofuro[3,2-*d*]isochromene (6n):

Pale yellow liquid; Yield 143 mg, 84% ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.18 (d, *J* = 1.3 Hz, 1H), 6.90 (d, *J* = 1.2 Hz, 1H), 4.60 (d, *J* = 10.9 Hz, 1H), 4.06 (dd, *J* = 1.5, 12.3 Hz, 1H), 3.99 (td, *J* = 3.2, 8.8 Hz, 1H), 3.89 (q, *J* = 8.6 Hz, 1H), 3.85 (dd, *J* = 3.3, 12.3 Hz, 1H), 2.41-2.31 (m, 1H), 2.09-2.01 (m, 1H), 1.96 (td, *J* = 5.1, 13.4 Hz, 1H), 1.85 (dd, *J* = 5.0, 10.9 Hz, 1H), 1.79-1.73 (m, 1H), 1.72-1.60 (m, 3H), 1.48-1.42 (m, 1H), 1.30-1.18 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.2, 127.6, 122.2, 108.8, 79.5, 75.8, 66.5, 64.9, 45.0, 42.8, 32.2, 28.0, 22.8, 22.6, 20.9. IR (KBr): υ 2920, 2851, 1458, 1219, 1106, 1029, 772, 600; HRMS(EI) calcd for $C_{15}H_{19}BrO_2S$ $[M]^+$: 342.0289. Found: 342.0280.

6-Phenyloctahydro-2*H*-cyclopenta[*c*]furo[2,3-*d*]pyran (6o):

Pale yellow liquid; Yield 97 mg, 80%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36-7.26 (m, 5H), 4.13 (d, *J* = 12.2 Hz, 1H), 3.97-3.86 (m, 2H), 3.79-3.34 (m, 2H), 2.39-2.30 (m, 1H), 2.18-2.08 (m, 3H), 2.06-1.98 (m, 1H), 1.87-1.64 (m, 4H), 1.29-1.20 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.8, 128.3, 127.8, 127.3, 89.7, 83.4, 66.9, 64.9, 47.3, 40.1, 34.3, 29.4, 25.9, 21.7; IR (KBr): υ 2921, 2850, 1453, 1218, 1112, 1029, 771, 749, 605; HRMS(EI) calcd for $C_{16}H_{20}O_2$ $[M]^+$: 244.1463 Found: 244.1460.

6-*p*-Tolyloctahydro-2*H*-cyclopenta[*c*]furo[2,3-*d*]pyran (6p):

Pale yellow liquid; Yield 105 mg, 82%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.22 (d, *J* = 7.9 Hz, 2H), 7.14 (d, *J* = 7.7 Hz, 2H), 4.11 (d, *J* = 12.0 Hz, 1H), 3.96-3.86 (m, 2H), 3.75 (dd, *J* = 2.7, 12.2 Hz,

1H), 3.72 (d, *J* = 11.2 Hz, 1H), 2.40-2.28 (m, 1H), 2.33 (s, 3H), 2.17-2.07 (m, 3H), 2.05-1.97 (m, 1H), 1.87-1.68 (m, 3H), 1.27-1.19 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.9, 137.5, 129.0, 127.3, 89.8, 83.3, 66.9, 64.9, 47.1, 40.2, 34.4, 29.4, 26.0, 21.8, 21.0. IR (KBr): υ 2952, 2921, 1515, 1453, 1218, 1111, 1031, 809, 771 HRMS (Orbitrap ESI) calcd for $C_{17}H_{23}O_2$ $[M+H]^+$: 259.1692. Found: 259.1689.

6-(4-Bromophenyl)octahydro-2*H*-cyclopenta[*c*]furo[2,3-*d*]pyran (6q):

Pale yellow liquid; Yield 135 mg, 84%; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.47 (d, *J* = 8.3 Hz, 2H), 7.21 (d, *J* = 8.3 Hz, 2H), 4.11 (d, *J* = 12.2 Hz, 1H), 3.95-3.86 (m, 2H), 3.74 (dd, *J* = 2.7, 12.3 Hz, 1H), 3.72 (d, *J* = 10.9 Hz, 1H), 2.36-2.26 (m, 1H), 2.18-2.08 (m, 2H), 2.05-1.95 (m, 2H), 1.87-1.68 (m, 4H), 1.22-1.15 (m, 1H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.0, 131.4, 129.0, 121.7, 89.5, 82.7, 66.9, 64.9, 47.2, 40.0, 34.3, 29.4, 25.6, 21.8. IR (KBr): υ 2952, 2870, 1591, 1488, 1218, 1112,1006, 815, 772; HRMS(EI) calcd for $C_{16}H_{19}BrO_2$ $[M]^+$: 322.05684 Found: 322.05680.

6-(4-Chlorophenyl)octahydro-2*H*-cyclopenta[*c*]furo[2,3-*d*]pyran (6r):

Pale yellow liquid; Yield 118 mg, 86%; ^{1}H NMR (300 MHz, $CDCl_3$): δ7.33-7.30 (m, 2H), 7.28-7.25 (m, 2H), 4.11 (d, *J* = 12.2 Hz, 1H), 3.95-3.86 (m, 2H), 3.77-3.71 (m, 2H), 2.36-2.26 (m, 1H), 2.18-2.08 (m, 2H), 2.06-1.95 (m, 2H), 1.87-1.68 (m, 4H), 1.23-1.15 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.4, 133.5, 128.7, 128.4, 89.5, 82.6, 66.9, 64.9, 47.3, 40.0, 34.3, 29.4, 25.8, 21.9. IR (KBr): υ 2956, 2851, 1491, 1217, 1089, 1011, 819, 748; HRMS(EI) calcd for $C_{16}H_{19}ClO_2$ $[M]^+$: 278.1073 Found: 278.1070.

4-Phenyl-6-*p*-tolyldecahydrofuro[3,2-*d*]isochromene (10a):

White solid; m.p. 140-142 °C. Yield 165 mg, 95%; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38-7.34 (m, 2H), 7.32-7.27 (m, 4H), 7.23-7.16 (m, 3H), 4.93 (d, *J* = 3.0 Hz, 1H), 4.56 (d, *J* = 11.1 Hz, 1H), 3.94 (td, *J* = 2.8, 9.4 Hz, 1H), 3.80 (dd, *J* = 8.5, 17.2 Hz, 1H), 2.35 (s, 3H), 2.27-2.17 (m, 2H), 2.07-2.01 (m, 1H), 1.93-1.88 (m, 1H), 1.78-1.57 (m, 4H), 1.51-1.31 (m, 3H), 1.13 (d, *J* = 13.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.6, 138.0, 137.3, 128.9, 128.0, 126.9, 126.7, 125.1, 80.7, 80.4, 76.3, 64.8, 50.8, 41.7, 32.4, 25.3, 23.1, 22.3, 21.1, 21.1; IR (neat): υ 2932, 2860,

1540, 1141, 1068, 1029, 814, 752, 700; HRMS(EI) calcd for $C_{24}H_{28}O_2$ $[M]^+$: 348.2089 Found: 348.2079.

Crystal Data for 10a: $C_{24}H_{28}O_2$ (M =348.46): monoclinic, space group $P2_1/c$ (no. 14), a = 18.4384(16) Å, b = 8.3568(7) Å, c = 13.1820(11) Å, β = 108.980(1)°, V = 1920.7(3) Å^3, Z = 4, T = 294.15 K, μ(MoKα) = 0.075 mm^{-1}, *Dcalc* = 1.205 g/mm^3, 21823 reflections measured (4.672 ≤ 2Θ ≤ 56.656), 4619 unique (R_{int} = 0.0244) which were used in all calculations. The final R_1 was 0.0532 (I > 2σ(I)) and wR_2 was 0.1466 (all data) CCDC 1423578 contains supplementary Crystallographic data for the structure. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

4-Phenyl-6-styryldecahydrofuro[3,2-*d*]isochromene (10b):

White solid; m.p. 145-147 °C. Yield 162 mg, 90% ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.44-7.41 (m, 2H), 7.38-7.29 (m, 6H), 7.26-7.20 (m, 2H), 6.67 (d, J = 15.8 Hz, 1H), 6.25 (dd, J = 7.4 Hz, 15.8, 1H), 4.87 (d, J = 3.0 Hz, 1H), 4.25 (dd, J = 7.7, 9.9 Hz, 1H), 3.91 (td, J = 2.8, 9.4 Hz, 1H), 3.78 (dd, J = 8.5, 16.7 Hz, 1H), 2.18-2.08 (m, 2H), 2.02-1.96 (m, 1H), 1.82-1.06 (m, 6H), 1.53-1.40 (m, 2H), 1.34-1.24 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 141.5, 136.7, 132.5, 128.6, 128.4, 128.09, 127.6, 126.8, 126.5, 125.1, 80.0, 79.8, 76.0, 64.7, 50.7, 40.2, 32.5, 25.2, 23.0, 22.5, 20.9; IR (neat): υ 3026, 2930, 2860, 1494, 1449, 1214, 1138, 1066, 1028, 964, 843, 748, 694; HRMS(EI) calcd for $C_{25}H_{28}O_2$ $[M]^+$: 360.2089 Found: 360.2075.

Methyl 4-(4-phenyldecahydrofuro[3,2-*d*]isochromen-6-yl)benzoate (10c):

White solid; m.p. 148-150 °C. Yield 137 mg, 70% ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.07-8.04 (m, 2H), 7.50-7.47 (m, 2H), 7.38-7.30(m, 4H), 7.25-7.21 (m, 1H), 4.95 (d, J = 3.0 Hz, 1H), 4.66 (d, J = 10.9 Hz, 1H), 3.94 (td, J = 2.7, 9.3 Hz, 1H), 3.92 (s, 3H), 3.81 (dd, J =8.6, 16.9 Hz, 1H), 2.29-2.17 (m, 2H), 2.10-2.04 (m, 1H), 1.89 (dd, J = 4.8, 10.8 Hz, 1H), 1.8-1.59 (m, 4H), 1.54-1.46 (m, 2H), 1.43-1.34 (m, 1H), 1.07(d, J =14.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 166.8, 146.1, 141.2, 129.65, 128.1, 126.9, 125.0, 80.4, 80.2, 76.5, 64.9, 52.0, 50.8, 41.9, 32.4,

25.3, 23.0, 22.2, 21.1; IR (neat): υ 2931, 2861, 1719, 1611, 1437, 1275, 1107, 1069, 1028, 751, 704; HRMS(EI) calcd for $C_{25}H_{28}O_4$ $[M]^+$: 392.1987 Found: 392.1977.

4-(4-(4-Methoxyphenyl)decahydrofuro[3,2-*d*]isochromen-6-yl)-*N*,*N*-diphenylaniline (10d):

Pale yellow solid; m.p. 220-222 °C. Yield 199 mg, 75% ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31-7.21 (m, 8H), 7.12-7.04 (m, 6H), 7.03-6.97 (m, 2H), 6.88-6.83 (m, 2H), 4.88 (d, *J* = 2.93 Hz, 1H), 4.55 (d, *J* = 11.0 Hz, 1H), 3.94 (td, *J* = 2.4, 9.2 Hz, 1H), 3.80 (dd, *J* = 8.4, 14.9 Hz, 1H), 3.78 (s, 3H), 2.3-2.13 (m, 2H), 2.03-1.95 (m, 1H), 1.93-1.86 (m, 1H), 1.8-1.43 (m, 6H), 1.43-1.18 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 158.4, 147.7, 147.2, 135.3, 133.8, 129.1, 127.8, 126.34, 124.1, 123.9, 122.6, 113.4, 80.5, 80.4, 76.2, 64.8, 55.2, 51.0, 41.7, 32.4, 29.6, 25.4, 23.1, 22.4, 21.1; IR (neat): υ 2928, 2857, 1589, 1510, 1490, 1276, 1246, 1174, 1069, 1032, 832, 753, 696; HRMS(EI) calcd for $C_{36}H_{37}NO_3$ $[M]^+$: 531.2773 Found: 531.2770.

6-(Biphenyl-4-yl)-4-*p*-tolyldecahydrofuro[3,2-*d*]isochromene (10e):

White solid; m.p. 155-157 °C. Yield 192 mg, 91% ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.64-7.56 (m, 4H), 7.50-7.40 (m, 4H), 7.38-7.33 (m, 1H), 7.30-7.24 (m, 2H), 7.16-7.10 (m, 2H), 4.93 (d, *J* = 2.4 Hz, 1H), 4.64 (d, *J* = 11.1 Hz, 1H), 3.96 (td, *J* = 2.6, 9.2 Hz, 1H), 3.82 (dd, *J* = 8.3, 16.8 Hz, 1H), 2.32 (s, 3H), 2.29-2.19 (m, 2H), 2.09-2.00 (m, 1H), 1.95 (dd, *J* = 4.3, 10.5 Hz, 1H), 1.81-1.33 (m, 7H), 1.20 (d, *J* = 13.9 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 140.9, 140.6, 140.1, 138.5, 136.32, 128.7, 128.7, 127.4, 127.1, 127.0, 125.0, 80.6, 80.4, 76.3, 64.8, 50.9, 41.8, 32.5, 25.4, 23.1, 22.4, 21.19, 21.0; IR (neat): υ 2930, 2860, 1514, 1486, 1451, 1140, 1099, 1070, 1032, 968, 833, 752, 696; HRMS(EI) calcd for $C_{30}H_{32}O_2$ $[M]^+$: 424.24023 Found: 424.24020.

6-(3-(Benzyloxy)propyl)-4-*p*-tolyldecahydrofuro[3,2-*d*]isochromene (10f):

Pale yellow liquid; Yield 178 mg, 85% ; ^{1}H NMR (500 MHz, $CDCl_3$): 7.36-7.31 (m, 4H), 7.3-7.26 (m, 1H), 7.22-7.18 (m, 2H), 7.14-7.10 (m, 2H), 4.67 (d, *J* = 2.2 Hz, 1H), 4.52 (ABq, *J* = 12.0 Hz, 2H), 3.85 (td, *J* = 3.0, 9.1 Hz, 1H), 3.74 (dd, *J* = 5.4, 13.7 Hz, 1H), 3.63-3.57 (m, 1H), 3.53 (t, *J* = 6.4 Hz, 2H), 2.33 (s, 3H), 2.1-1.71 (m, 7H), 1.70-1.60 (m, 4H), 1.60-1.51 (m, 2H), 1.47 (d, *J* = 13.2 Hz, 1H), 1.43-1.37 (m, 1H), 1.24-1.13 (m, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 139.0, 138.6, 136.1, 128.7, 128.3, 127.6, 127.4, 124.9, 80.4, 76.5, 75.6, 72.8, 70.4, 64.7, 50.6,

39.8, 32.5, 29.4, 25.2, 25.2, 23.2, 22.3, 21.0, 20.9; IR (neat): υ 2929, 2858, 1514, 1451, 1095, 1067, 1028, 738, 696; HRMS(EI) calcd for $C_{28}H_{36}O_3$ $[M]^+$: 420.2664 Found: 420.2660.

6-(2-(Benzyloxy)ethyl)-4-propyldecahydrofuro[3,2-*d*]isochromene (10g):

Pale yellow liquid; Yield 134 mg, 75% ; ^{1}H NMR (500 MHz, $CDCl_3$): 7.35-7.32 (m, 4H), 7.31-7.27 (m, 1H), 4.56-4.47 (m, 2H), 3.91 (td, *J* =3.0, 8.6 Hz, 1H), 3.83 (dd, *J* =8.3, 16.7 Hz, 1H), 3.68-3.59 (m, 2H), 3.56-3.49 (m, 2H), 2.10-1.99 (m, 2H), 1.96-1.89 (m, 1H), 1.86-1.78 (m, 1H), 1.77-1.66 (m, 1H), 1.66-1.39 (m, 10H), 1.36-1.24 (m, 2H), 1.20-1.10 (m, 1H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 138.6, 128.2, 127.5, 127.3, 80.4, 74.5, 73.9, 72.9, 67.1, 64.8, 49.1, 40.9, 36.3, 33.2, 32.4, 24.6, 23.1, 22.4, 20.8, 19.2, 14.0; IR (neat): υ 2930, 2862, 1453, 1361, 1091, 1030, 737, 697; HRMS(EI) calcd for $C_{23}H_{34}O_3$ $[M]^+$: 358.2507 Found: 358.2500.

4-Ethyl-6-*p*-tolyldecahydrofuro[3,2-d]isochromene (10h):

White solid; m.p. 92-94 °C. Yield 142 mg, 95% ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21-7.17 (m, 2H), 7.16-7.12 (m, 2H), 4.33 (d, *J* = 10.9 Hz, 1H), 3.99 (td, *J* = 2.8, 8.8 Hz, 1H), 3.90 (dd, *J* = 8.3, 16.9 Hz, 1H), 3.61 (td, *J* = 2.7, 6.8 Hz, 1H), 2.33 (s, 3H), 2.31-2.25 (m, 1H), 2.04 (td, *J* = 5.1, 13.4 Hz, 1H), 1.95-1.88 (m, 1H), 1.80 (dd, *J* = 5.1, 10.9 Hz, 1H), 1.74-1.42 (m, 7H), 1.42-1.22 (m, 2H), 1.05 (d, *J* = 14.2 Hz, 1H), 0.92 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.2, 137.1, 128.9, 126.9, 80.5, 80.4, 77.3, 76.6, 64.9, 48.3, 41.7, 32.4, 27.2, 24.4, 23.0, 22.4, 21.0, 10.3; IR (neat): υ 2929, 2860, 1514, 1454, 1368, 1166, 1078, 1032, 996, 963, 863, 813; HRMS(EI) calcd for $C_{20}H_{28}O_2$ $[M]^+$: 300.20893 Found: 300.20890.

Preparation of compounds 3 and 4.

To the ice-cooled solution of NaH (12 mmols) in 20 ml THF was added a solution diethyl-succinate (6 mmols) in THF and stirred for 10 min, 1 drops EtOH was added to initiate the reaction. After 10 min cyclohexanone or cyclopentanone (6 mmols) was added dropwise over 1 h and the reaction mixture was stirred for 12 h at rt. The reaction was quenched with 4 M HCl and extracted with EtOAc (3 × 20 mL). Combined organic layers were dried over Na_2SO_4,

filtered, and the solvent was removed under vacuo. The resulting brown syrup was dissolved in EtOH (20 mL) and acidified with conc H_2SO_4 and stirred for 1 h at 0 °C. The reaction mixture was warmed up to rt and refluxed for 12 h. The reaction mixture was quenched with saturated solution of $NaHCO_3$ and extracted with EtOAc (3 × 20 mL). The combined organic layers were dried (Na_2SO_4), filtered, and the solvent was removed in vacuo . The crude solution of diester was added to the solution of LAH (24 mmol) at 0 ^oC. Reaction mixture stirred at same temp for 30 min. After consumption of starting material reaction was quenched with sat NH4Cl and filtered over celite and washed with hot ethyl acetate. Filtrate was dried over Na_2SO_4 and evaporated on under vacuum. Residue was purified using column chromatography.

2-cyclopentenylbutane-1,4-diol (3):

Pale yellow liquid; Yield 673 mg, 72 %; ^1H NMR (500 MHz, $CDCl_3$): 5.55 (S, 1H), 3.75-3.70 (m, 1H), 3.67-3.55 (m, 3H), 2.62-2.55 (m, 1H), 2.36-2.31 (m, 2H), 2.29-2.23 (m, 2H), 1.91-1.84 (m, 2H), 1.75-1.69 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 144.32, 126.68, 64.6, 61.2, 41.5, 33.4, 32.3, 32.2, 23.1. IR (KBr): 3312, 2923, 2875, 2857, 1660, 1438, 1218, 1046, 1026, 918, 771; HRMS (ESI-Orbitrap) calcd for $C_9H_{17}O_2$ [M+H]+: 157.1223 Found: 157.1222.

2-cyclohexenylbutane-1,4-diol (4):

Pale yellow liquid; Yield 693 mg, 68 % ; ^1H NMR (500 MHz, $CDCl_3$): δ 5.58 (S, 1H), 3.72-3.67 (m,1H), 3.65-3.59 (m, 1H), 3.57 -3.48 (m, 2H), 2.32-2.26 (m, 1H), 2.06-2.01 (m, 2H), 1.98-1.88 (m, 2H), 1.69-1.58 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ 137.2, 124.6, 64.5, 61.3, 47.4, 32.9, 25.2, 25.2, 22.8, 22.5; IR (neat): υ 3335, 2927, 2884, 2852, 1700, 1676, 1608, 1436, 1218, 1025, 770; HRMS (ESI Orbitrap) calcd for $C_{10}H_{18}O_2Na$ [M+Na]+: 193.1190 Found: 193.1202.

Preparation of compounds 9a-e.

To the solution of compound 7 (2 mmol) in DCM was added 1.5 M solution of DIBAL-H (2 ml) at -78 ^{o}C and reaction mixture was stirred at same temp for 1 h. After consumption of starting material as evident by TLC reaction was quenched with 20 ml saturated solution of tartaric acid and stirred at rt for 30 min. Organic layer was separated and aq layer was extracted with DCM (3 × 10 mL) . Oranic layer was dried over Na_2SO_4 and evoparated under vaccum. Crude lactol was taken in 10 ml dry THF and to it was added 4 mmol of RMgBr (R=Ethyl, Propyl, Phenyl, *p*-Tolyl, p-Anisyl) at 0 ^{o}C and reaction was stirred for 2 h. Reaction was quenched with saturated NH_4Cl and extracted with ethyl acetate. Oranic layer was dried over Na_2SO_4 and crude material was purified by colum chromatography.

2-cyclohexenyl-1-phenylbutane-1,4-diol (9a):

Pale yellow liquid; Yield 393 mg, 80 % ; ^{1}H NMR (500 MHz, $CDCl_3$): δ7.32-7.21 (m, 5H), 5.37 (s, 1H), 4.60 (d, *J* = 7.6 Hz, 1H), 3.70-3.65 (m, 1H), 3.59-3.53 (m, 1H), 2.36-2.31 (m, 1H), 2.00-1.67 (m, 6H), 1.47-1.38 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 143.5, 137.4, 127.9, 127.3, 126.6, 124.5, 76.7, 61.8, 52.6, 32.5, 27.4, 25.2, 22.8, 22.3; IR (neat): υ 3328, 2922, 1661, 1450, 1346, 1012, 917, 756, 698; HRMS (ESI Orbitrap) calcd for $C_{16}H_{22}O_2Na$ [M+Na]+: 269.1512 Found: 269.1514.

2-cyclohexenyl-1-p-tolylbutane-1,4-diol (9b)

Pale yellow liquid; Yield 426 mg, 82 % ; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.21 -7.07 (m, 4H), 5.38 (s, 1H), 4.58 (d, *J* =7.5 Hz, 1H), 3.73-3.63 (m, 1H), 3.61-3.51 (m, 1H), 2.33 (s, 3H), 2.03-1.63 (m, 7H), 1.51-1.37 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 140.3, 137.5, 136.7, 128.6, 126.3, 124.3, 76.4, 61.8, 52.4, 32.3, 27.3, 25.1, 22.8, 22.3, 21.1; IR (neat): υ 3328, 2922, 1450, 1346, 1012, 917, 756, 698; HRMS (ESI Orbitrap) calcd for $C_{17}H_{24}O_2Na$ [M+Na]+: 283.1674 Found: 283.1671.

2-cyclohexenyl-1-(4-methoxyphenyl)butane-1,4-diol (9c)

Pale yellow liquid; Yield 469 mg, 85 % ; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.36 (s, 1H), 4.56 (d, *J* = 7.8 Hz, 1H), 3.80 (s, 3H), 3.76-3.66 (m, 1H), 3.62-3.53 (m, 1H), 2.36-2.28 (m, 1H), 2.03-1.94 (m, 1H), 1.91-1.60 (m, 5H), 1.48-1.36 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 158.7, 137.5, 135.5, 127.6, 124.4, 113.2, 76.3, 61.8, 55.1, 52.65, 32.7, 27.2, 25.1, 22.8, 22.3; IR (neat): υ 3336, 2923, 1611, 1511, 1440, 1242, 1174, 1030, 828, 752; HRMS (ESI Orbitrap) calcd for $C_{17}H_{25}O_3$ [M+H]+: 277.1803 Found: 277.1809.

3-cyclohexenylhexane-1,4-diol (9d)

Pale yellow liquid; Yield 376 mg, 95 % ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.51-5.48 (m, 1H), 3.72-3.65 (m, 1H), 3.61-3.54 (m, 1H), 3.48-3.41 (m, 1H), 2.06-1.89 (m, 5H), 1.83-1.74 (m, 1H), 1.72-1.51 (m, 6H), 1.35-1.25 (m, 1H), 0.96 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 138.1, 123.7, 74.6, 61.7, 51.5, 32.7, 28.1, 25.9, 25.2, 22.9, 22.5, 10.0; IR (neat): υ 3310, 2922, 2876, 1443, 1042, 969, 800; HRMS (ESI Orbitrap) calcd for $C_{12}H_{23}O_2$ [M+H]+: 199.1692 Found: 199.1694.

3-cyclohexenylheptane-1,4-diol (9e)

Pale yellow liquid; Yield 381 mg, 90 % ; ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.50 (s, 1H), 3.72-3.66 (m, 1H), 3.61-3.50 (m, 2H), 2.06-1.88 (m, 6H), 1.84-1.75 (m, 1H), 1.73-1.43 (m, 6H), 1.38-1.25 (m, 2H), 0.92 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 138.0, 123.7, 73.0, 61.8, 51.6, 37.4, 32.1, 25.2, 25.0, 22.9, 22.5, 18.9, 14.0; IR (neat): υ 3329, 2926, 2871, 1447, 1216, 1123, 1049, 998, 918, 752; HRMS (ESI Orbitrap) calcd for $C_{13}H_{25}O_2$ [M+H]+: 213.1849 Found: 213.1850.

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Supporting Information Available

NOESY and DQFCOSY study of **6a**, ORTEP diagram for compound **10a**, copies of ^{1}H and ^{13}C NMR spectra of products (**6a-r**,**10a-h**, **3**, **4, and 9a-e**) are provided in supporting information. This material is available free of charge via the internet at http://pubs.acs.org

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